Journal of Medical Virology 56:1–3 (1998)

Commentary

Clinical Implications of GB Virus C

Isa K. Mushahwar[1] and Jane N. Zuckerman[2]*

[1]*Virus Discovery Group, Abbott Laboratories, North Chicago, Illinois*
[2]*WHO Collaborating Centre for Reference and Research on Viral Diseases, Royal Free Hospital School of Medicine, London, England*

KEY WORDS: GBV-C; clinical features; hepatitis; liver disease

The predominant route of transmission of GBV-C appears to be parenteral by contaminated blood and blood products. However, since recent reports have shown that human saliva [Chen et al., 1997] and semen [Semprini et al., 1998] of GBV-C-infected individuals are positive for GBV-C RNA, the possibility exists that both of these routes may play a key role in the wide spread of GBV-C infections. In addition, perinatal or vertical transmission cases of GBV-C from infected mothers to newborns have been reported [Feucht et al., 1996; Fischler et al., 1997]. Current epidemiological data [Simons et al., 1996] show the presence of GBV-C RNA in sera obtained from a variety of sources. These include sera from hemophiliacs, thalassemic patients, intravenous drug abusers, multiply transfused individuals, transfusion-associated hepatitis cases, volunteer blood donors with both normal and elevated serum transaminase levels, hepatitis B (HBV) and hepatitis C (HCV) carriers, acute and patients with chronic non-A–E hepatitis, kidney, liver, and bone marrow transplant recipients and donors, patients with fulminant hepatitis, and patients treated by maintenance hemodialysis. Examination of serum specimens collected from healthy volunteer blood donors from different parts of the world confirmed the presence of GBV-C RNA in a remarkable 1–4% of the specimens [Dawson et al., 1996; Fiordalisi et al., 1996; Masuko et al., 1996; Moaven et al., 1996; Stark et al., 1996; Wu et al., 1996]. The infection is thus spread worldwide in healthy and diseased populations.

Most GBV-C infections appear to be asymptomatic, transient, and self-limiting, with slight or no elevation of alanine aminotransferase (ALT) levels. Most of these subclinical cases resolve after loss of serum GBV-C RNA with a concomitant appearance of antibody to the envelope E2 of GBV-C (anti-GBV-C E2 antibody) as reported by several investigators [Dille et al., 1996; Gutierrez et al., 1997]. These types of GBV-C infections are hardly noticeable and very difficult to evaluate when studied in multitransfused patients and/or patients in association with or superimposed on HBV or HCV infection.

GB virus C is capable of inducing persistent infection in about 5–10% of GBV-C-infected individuals. Masuko et al. [1996] followed retrospectively eight hemodialysis patients with GBV-C infection for 7–16 years. In two patients, the virus was present at the start of hemodialysis. One had a history of transfusion, and GBV-C RNA persisted over a period of 16 years, the other cleared GBV-C RNA after 10 years. In five patients, GBV-C RNA was first detected 3–20 weeks after blood transfusion and persisted for up to 13 years. A recent study by Charlton et al. [1998] has shown that hepatitis occurs in 60% of patients infected persistently with GBV-C/HGV transplanted for cryptogenic cirrhosis. Elucidating the viral mechanisms that lead to the establishment and maintenance of the persistent state is very crucial for the understanding of the pathogenesis of GBV-C.

The role of GBV-C in the etiology of fulminant hepatitis is not yet fully established. Further studies are required to establish a definite link between fulminant hepatitis and GBV-C infection. One study in Japan [Yoshiba et al., 1995] documented the presence of GBV-C RNA in three of six patients with fulminant hepatitis without evidence of infection with known hepatitis viruses. Since that report, questions were raised concerning the association of GBV-C with acute liver failure [Alter, 1996]. Specifically, of whether GBV-C was an "innocent bystander" transmitted by transfusions given to the three patients prior to the onset of fulminant hepatitis. Additional studies [Yoshiba et al., 1996], however, showed that only few of the 63 fulminant hepatitis patients studied so far had received blood transfusion prior to the onset of fulminant hepatitis, but definitely not all. In a similar study also carried out in Japan [Tameda et al., 1996], GBV-C

*Correspondence to: Jane N. Zuckerman, WHO Collaborating Centre for Reference and Research on Viral Diseases, Royal Free Hospital School of Medicine, London NW3 2PF, England.

Accepted 6 April 1998

RNA was detected in three (20%) of 15 patients with HBV infection and three (12%) of 25 patients without markers of hepatitis A–E infection. Overall, GBV-C RNA was detected in six of 44 (14%) patients with fulminant hepatitis at a frequency significantly higher ($P < 0.001$) than that in three of 326 (0.9%) blood donors matched for age with the patients. Of the six patients with GBV-C RNA, only three had a history of transfusion and all of these patients were coinfected with HBV. These results, according to Tameda et al. [1966], indicate a role of GBV-C in inducing fulminant hepatitis either by itself or in concert with other hepatitis viruses.

A unique study [Fiordalisi et al., 1996] showing histological features in liver biopsies from patients infected with GBV-C alone has been reported. GBV-C was implicated in a significant number of acute and chronic cases of non-A–E hepatitis. Among the six chronic hepatitis patients with GBV-C RNA, the histology of the liver samples revealed chronic active hepatitis in one patient and chronic persistent hepatitis in five others. All patients with chronic hepatitis had elevated ALT levels between 89 and 478 U/L. In contrast, among the 11 acute hepatitis cases positive for GBV-C RNA, the ALT levels varied between 615 and 2477 U/L.

Colombatto et al. [1996] studied GBV-C in 67 patients with liver disease without any markers for hepatitis A–E. They reported that the spectrum of liver disease associated with GBV-C infection in these patients is wide, with a variety of histological liver lesions ranging from steatosis to fibrosis and cirrhosis. In particular, nonspecific inflammatory bile duct lesions were found in 50% of patients with only GBV-C infection. They also suggest that GBV-C infection is present significantly more often with elevated cholestatic enzymes, namely, gamma glutamyl transpeptidase and alkaline phosphatase. Similar studies have been reported by Ross et al. [1997] who showed that GBV-C infection might affect the clinical course and outcome after orthotopic liver transplantation (OLT) by the development of severe cholestasis, which could result from bile duct damage and bile duct loss. Such damage was also observed in the grafts of GBV-C-positive liver organ transplant recipients by Dhillon et al. [1996]. Ross et al. [1997] further state that although prospective clinical trials are needed to understand fully this issue, a possible association of GBV-C with complicated unexplained cholestatic courses after liver transplantation would add an important new facet to the clinical profile of GBV-C infections.

In this context, studies on the association between recurrent or de novo GBV-C infection and severe post-transplant cholestasis and ductopenia have been extended [G. Dusheiko, personal communication]. These studies confirmed that a large number of patients with chronic cholestasis are indeed positive for GBV-C. However, a large number of GBV-C-positive transplant recipients have no evidence of similar ductopenia and the significance and specificity of the association require further investigation since a similar appearance could result from rejection or other factors including HLA mismatch, antirejection therapy, infection with cytomegalovirus, as well as concurrent infections [G. Dusheiko, personal communication].

The above studies indicate the importance of studying patients with GBV-C RNA without concomitant HBV or HCV coinfection.

Numerous studies have shown that in HCV-coinfected individuals, GBV-C does not seem to affect HCV replication, HCV RNA concentration, and liver disease. On the other hand, other studies have shown different results. Recent studies by Manolakopoulos et al. [1998] showed the influence of GBV-C viremia on the clinical, virological, and histological features of early hepatitis C-related hepatic disease. It was found that although coinfection with GBV-C did not alter the biochemical and virological profile of patients with HCV hepatitis, there was an association between GBV-C and HCV viremia and portal and periportal inflammation. It was noted that the duration of HCV/GBV-C coinfection may be an important factor in progression of liver disease. It was also observed that inflammation with necrosis in the portal and periportal tracts was significantly higher in patients with combined viremia compared to those with HCV infection alone. These findings suggest that GBV-C in patients with HCV infection might accelerate liver injury. Finally, a trend was noted toward more severe fibrosis in patients with dual infection. Similarly, Diamantis et al. [1997] reported previously that virus load and ALT levels did not differ significantly in patients coinfected with HCV and GBV-C/HGV. However, mild fibrosis correlated with GBV-C/HGV coinfection.

An interesting study by Ellendrieder et al. [1998] indicated that HCV has no significance in the pathogenesis of non-Hodgkin's lymphoma in Germany. The increased prevalence of GBV-C/HGV (16.3%) in patients with low-grade non-Hodgkin's lymphoma could suggest a pathological consequence of GBV-C/HGV infection outside the liver. However, several reports have shown unequivocally the lack of association or involvement of GBV-C infection with other diseases. These included autoimmune liver disease, aplastic anemia, hepatocellular carcinoma, porphyria cutanea tarda, oral cancer, and oral lichen planus.

Based on incomplete scientific information at that time, many editorials and commentaries had appeared in the literature describing GBV-C as an "accidental tourist" or an "innocent bystander" and "a human orphan flavivirus" [Theodore and Lemon, 1997] with no association whatsoever with liver disease. More recent studies, however, do not support these commentaries and show (1) that GBV-C is involved with some cases of acute and chronic hepatitis [Fiordalisi et al., 1996]; (2) that GBV-C infects chimpanzees that are appropriate nonhuman primates for viral hepatitis studies [Bukh et al., 1998]; and (3) that GBV-C does indeed replicate in human liver as shown by in situ hybridization and

immunohistochemical staining [Mushahwar 1998; Mushahwar et al., 1998]. Results of further studies are awaited with interest as evidence is accumulating that GBV-C is not an orphan virus in search of disease.

REFERENCES

Alter HJ (1996): The cloning and clinical implications of HGV and HGBV-C. New England Journal of Medicine 334:1536–1537.

Bukh J, Kim JP, Govindarajan S, Apgar CL, Foung, SKH, Wages J, Yun AJ, Shapiro M, Emerson SU, Purcell RH (1998): Experimental infection of chimpanzees with hepatitis G virus and genetic analysis of the virus. Journal of Infectious Diseases 177:855–862.

Charlton MR, Brandhagen D, Wiesner RH, Gross JB, Detmer J, Collins M, Kolberg J, Krom RAF, Persing DH (1998): Hepatitis G virus infection in patients transplanted for cryptogenic cirrhosis. Transplantation 65:73–76.

Chen M, Sonnerborg A, Johansson B, Sallberg M (1997): Detection of Hepatitis G virus (GB virus C) RNA in human saliva. Journal of Clinical Microbiology 35:973–975.

Colombatto P, Randone A, Civitico G, Monti Gorin G, Dolci L, Medaina N, Galleri G, Oliveri F, Baldi M, Tappero G, Volpes R, David E, Verme G, Smedile A, Bonino F, Brunetto MR (1997): A new hepatitis C virus-like flavivirus in patients with cryptogenic liver disease associated with elevated GGT and alkeline phosphatase serum levels. Journal of Viral Hepatitis 4:55–60.

Dawson GJ, Schlauder GG, Pilot-Matias TJ, Theile D, Leary TP, Murphy P, Rosenblatt JE, Simons JN, Martinson FEA, Gutierrez RA, Lentino JR, Pachuki C, Muerhoff AS, Widell A, Tegtmeir G, Desai SM, Mushahwar IK (1996): Prevalence of GB virus C using reverse transcriptase-polymerase chain reaction. Journal of Medical Virology 50:97–103.

Dhillon AP, Savage K, Kim JS, Yun A, Burroughs AK, Rolles K, Dusheiko G (1996): Histopathology of hepatitis G virus infection. IX Triennial International Symposium on Viral Hepatitis and Liver Disease, Rome, Abstract C209.

Diamantis ID, Kouroumalis E, Koulentaki M, Falserkan E, Schmid PA, Hirsch HH, Buhler H, Gyr K, Battegay M (1997): Influence of HGV infection on liver disease. European Journal of Clinical Microbiology and Infectious Disease 16:916–919.

Dille BJ, Surowy TK, Gutierrez RA, Coleman RF, Knigge MF, Carrick RJ, Aach RD, Hollinger FB, Stevens CE, Barbosa LH, Nemo GJ, Mosley JW, Dawson GJ, Mushahwar IK (1997): An ELISA for detection of antibodies to the E2 protein of GB virus C. Journal of Infectious Diseases 175:458–461.

Ellenrieder V, Weidenbach H, Frickhofer N, Michel D, Prummer O, Klatt S, Bernas O, Mertens D, Adler G, Bekh K (1998): HCV and HGV in B-cell non-Hodgkin's lymphoma. Journal of Hepatology 28:34–39.

Feucht H-H, Zollner B, Polywka S, Laufs R (1996): Vertical transmission of hepatitis G. Lancet 347:615.

Fiordalisi G, Zanella I, Mantero G, Bettinardi A, Stellini R, Paraninfo G, Cadeo G, Primi D (1996): High prevalence of GB virus C infection in a group of Italian patients with hepatitis of unknown etiology. Journal of Infectious Diseases 174:181–183.

Fischler B, Lara C, Chen M, Sonnerborg A, Nemeth A, Sallberg M (1997): Genetic evidence for mother-to-infant transmission of hepatitis G virus. Journal of Infectious Diseases 176:281–285.

Gutierrez RA, Dawson GJ, Knigge MF, Melvin SL, Heynen CA, Kyrk CR, Young C, Carrick RJ, Schlauder GG, Surowy TK, Dille GJ, Coleman PF, Thiele DL, Lentino JR, Pachucki C, Mushahwar IK (1997): Seroprevalence of GB virus C and persistence of RNA and antibody. Journal of Medical Virology 53:167–173.

Manolakopoulos S, Morris A, Davies S, Brown D, Hajat S, Dusheiko G (1998): Influence of GB virus C viremia on the clinical, virological and histological features of early hepatitis C-related hepatic disease. Journal of Hepatology 28:173–178.

Masuko K, Mitsui T, Iwano K, Yamazaki C, Okuda K, Meguro T, Murayama N, Inoue T, Tsuda F, Okamoto H, Miyakawa Y, Mayumi M (1996): Infection with hepatitis GB virus C in patients on maintenance hemodialysis. New England Journal of Medicine 334:1485–1490.

Moaven LD, Hyland CA, Young IF, Bowden DS, Mccaw R, Mison L, Locarnini SA (1996): Prevalence of hepatitis G virus in Queensland blood donors. Medical Journal of Australia 165:369–371.

Mushahwar IK (1998): Tissue tropism of GBV-C and protective immunity of anti-GBV-C E2. VIII International Symposium on Viral Hepatitis, Madrid, Spain.

Mushahwar IK, Erker JC, Patterson BK, Desai SM (1998): Tissue tropism of GBV-C and HCV. Abstracts of the XIX U.S.–Japan Hepatitis Joint Panel Meeting, U.S.–Japan Cooperative Medical Science Program. Pacific Grove, CA.

Ross RS, Viazov S, Kruppenbacher JP, Elsner S, Sarr S, Lange R, Eigler F-W, Roggendorf M (1997): GB virus C infection in patients who underwent liver transplantation. Liver 17:238–243.

Semprini AE, Persico T, Thiers V, Oneta M, Tuveri R, Serafini P, Boschini A, Giuntelli S, Pardi G, Brechot C (1998): Absence of hepatitis C virus and detection of hepatitis G/GB virus C RNA sequences in the semen of infected. Journal of Infectious Diseases 177:848–854.

Simons JN, Desai SM, Mushahwar IK (1996): The GB viruses: Isolation, characterization, diagnosis and epidemiology. Viral Hepatitis Reviews 2:229–246.

Stark K, Bienzle U, Hess G, Engel AM, Hegenscheid B, Schluter V (1996): Detection of the hepatitis G virus genome among injecting drug users, homosexual and bisexual men, and blood donors. Journal of Infectious Diseases 174:1320–1323.

Tameda Y, Kosaka Y, Tagawa S, Takase K, Sawada N, Nakao H, Tsuda F, Tanaka K, Okamoto H, Miyakawa Y, Mayumi M (1996): Infection with GB virus C (GBV-C) in patients with fulminant hepatitis. Journal of Hepatology 25:842–847.

Theodore D, Lemon SM (1997): GB virus C, hepatitis G virus, or human orphan flavivirus? Hepatology 25:1285–1286.

Wu R-R, Mizokami M, Cao K, Nakano T, Ge X-M, Wang S-S, Orito E, Ohba K-I, Mukaide M, Hikiji K, Lau JYN, Iino S (1996): GB virus C/Hepatitis G virus infection in Southern China. Journal of Infectious Diseases 175:168–171.

Yoshiba M, Okamoto H, Mishiro S (1995): Detection of GBV-C hepatitis virus genome in serum from patients with fulminant hepatitis of unknown aetiology. Lancet 346:1131–1132.

Yoshiba M, Inoue K, Sekiyama K (1996): Hepatitis GB virus C. New England Journal of Medicine 335:1392–1393.